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FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

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HUYNH, PHUONG N	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 02092004

Application Number: 10/071,247
Filing Date: February 11, 2002
Appellant(s): GRIFFITHS, GARY L.

Stephen B. Maebius
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/12/03

(1) ***Real Party in Interest***

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because claims 10, 11, and 12 depend from claim 9. Further, the claimed method requires the bispecific antibody or antibody fragment with one arm that is specific to a target tissue of the patient and another arm that is specific to an F-18 labeled peptide. For these reasons, claims 9-12 and 16-20 should stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Kuby et al, 1994, Immunology, Second edition, pages 86-96.

Colman et al, 1994, A structural view of immune recognition by antibodies, pages 33-36.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 9-12 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for detecting a tissue in a patient by a) administering to a patient a bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to a specific F-18 labeled peptide such as the ones recited in claims 13-15 or a low molecular weight hapten conjugated to said F-18-labeled peptide and allowing the bispecific antibody or antibody fragment to bind to the target tissue and the non-targeted bispecific antibody or antibody fragment to clear, b) administering the F-18-labeled peptide such as the ones recited in claims 13-15 or the hapten conjugate thereof to the patient, and allowing said F-18 labeled peptide or the hapten conjugate thereof to bind to the bispecific antibody or the antibody fragment, and the unbound F-18-labeled peptide or hapten conjugate thereof to clear, and c) detecting the F-18-labeled peptide thereby detecting the target tissue by positron emission tomography, **does not** reasonably provide enablement for (1) a method for detecting a tissue comprising a) administering to a patient all bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to *all* F-18-labelde peptide or all low molecular weight hapten conjugated to *all* F-18-labeled peptide and allowing the bispecific antibody or antibody fragment to bind to the target tissue and the non-targeted bispecific antibody or antibody fragment to clear, b) administering *all* F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing said F-18 labeled peptide or the hapten conjugate thereof to bind to *all* bispecific antibody or the antibody fragment, and the unbound F-18-labeled peptide or hapten conjugate thereof to clear, and c) detecting the F-18-labeled peptide thereby detecting the target tissue, (2) the said method wherein the F-18-labeled peptide contains a thiol group, (3) the said method wherein the F-18-labeled peptide is labeled according to a method for radiolabeling a thiol-containing peptides with all fluorine-18 (F-18) comprising reacting all peptide comprising a free thiol group with a labeling reagent having the general formula 18F-(CH2)m-CR1R2-(CH2)n-X wherein n is 0, 1 or 2; m is 0, 1 or 2; and n+m is 0, 1 or 2; X is selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, unsubstituted maleimide, maleimide substituted with one or two alkyl groups and 3-sulfo-maleimide and R1 and R2 are the same or different are selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, hydrogen, CONH2, carboxyl, hydroxyl,

sulfonic acid, tertiary amine, quaternary ammonium, unsubstituted alkyl, substituted alkyl, -COOR', -CONR'2 or COR' wherein the substituents of the substituted alkyl groups are selected from the group consisting of -CONH2, carboxyl, hydroxyl, sulfonic acid, tertiary amine and quaternary ammonium and wherein R' is C1-C6 alkyl or phenyl, or a method for radiolabeling thiol-containing peptides with fluorine-18 (F-18), comprising reacting all peptide comprising a free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate ad triflate, (3) the said method wherein the hapten is all metal chelate complex, (4) the said method wherein the metal chelate complex comprises manganese, iron, or gadolinium, (5) the method mentioned above wherein the bispecific antibody or antibody fragment is *all* monoclonal *all* humanized antibody, and (6) the method mentioned above wherein the F-18-labeled peptide is detected by positron emission tomography. The specification does not enable all person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method for detecting a tissue using a specific bispecific or humanized monoclonal antibody or Fab fragment thereof where one arm is specific for a target tissue of the patient and the other arm is specific for an F-18-labeled peptide selected from the group consisting of X-Gly-D-Tyr-D-Trp-Gly-D-Lys(X)-Gly-D-Tyr-DTrp-OH where X represents a free or protected amino acid group, Ac-Cys(Y)-D-Tyr-D-Trp-Gly-D-Cys(Y)-Gly-Dtyr-D-Trp-OH wherein Y represents a free or protected thiol group, and Ac-Gly-D-iodo-Tyr-Trp-Gly-D-Lys(Ac)-Gly-D-Trp-OH by positron emission tomography (PET).

The specification does not teach how to make and use all bispecific or humanized monoclonal antibody or Fab fragment thereof where one arm is specific for *all* target tissue of the

patient and the other arm is specific for all undisclosed F-18-labeled peptide, all low molecular weight hapten conjugated to *all* F-18-labeled peptide mentioned above for a method for PET imaging. There is insufficient guidance with regard to the binding specificity, and affinity of all bispecific antibodies for the claimed method. Further, there are no vivo working examples demonstrating that all antibodies with unknown specificity would be useful for a method of detecting a tissue in a patient using PET. Other than the specific F-18 labeled peptides mentioned above, there is insufficient guidance about the structure (amino acid residues) of all of F-18 labeled peptide, in turn, would be useful for making the bispecific antibody for the claimed method. Without the specific amino acid residues, one of skilled in the art cannot even contemplate of making such bispecific antibody that would have one arm specific for all F-18 labeled peptide and one arm would be specific for all tissue in a patient. Given the indefinite number of undisclosed bispecific antibody, it is unpredictable which undisclosed bispecific antibody would bind specifically to all undisclosed F-18 peptide and a target tissue for the claimed method.

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Colman *et al* teach that even a single amino acid changes within the interface of an antibody-antigen can raise or lower the affinity of the antibody (See page 33, in particular).

Given the indefinite number of undisclosed bispecific antibody and F-18 labeled peptide, it is unpredictable which undisclosed bispecific antibody would bind specifically to the undisclosed F-18 labeled peptide, in turn, would be useful for all purpose. Since the F-18 labeled peptide without the specific amino acid is not enabled, it follows that *all* low molecular weight hapten conjugated to *all* undisclosed F-18 labeled peptide for making the bispecific antibody that would bind specifically to all undisclosed F-18 labeled peptide, in turn, useful for the claimed method is not enabled. Since the binding specificity of the bispecific antibody such as monoclonal, humanized or antibody fragment thereof in the claimed method is not enabled, it follows that the method of detecting wherein the F-18 peptide contains a thiol group, or the labeled peptide is labeled by the method as set forth in claims 11 or 12 or the hapten conjugated F-18 labeled peptide wherein the hapten is a metal chelate complex such as metal chelate complex comprising manganese, iron, or gadolinium is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

2. Claims 9-12 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method for detecting a tissue comprising a) administering to a patient *all* bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to *all* F-18-labelde peptide or all low molecular weight hapten conjugated to *all* F-18-labeled peptide and allowing the bispecific antibody or antibody fragment to bind to the target tissue and the non-targeted bispecific antibody or antibody fragment to clear, b) administering *all* F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing said F-18 labeled peptide or the hapten conjugate thereof to bind to *all* bispecific antibody or the antibody fragment, and the unbound F-18-labeled peptide or hapten conjugate thereof to clear, and c) detecting the F-18-labeled peptide thereby detecting the target tissue, (2) the said method wherein the F-18-labeled peptide contains a thiol group, (3) the said method wherein the F-18-labeled peptide is labeled according to a method for radiolabeling a thiol-containing peptides with all fluorine-18 (F-18) comprising reacting all peptide comprising a free thiol group with a labeling reagent having the general formula 18F-(CH2)m-CR1R2-(CH2)n-X wherein n is 0, 1 or 2; m is 0, 1 or 2; and n+m is 0, 1 or 2; X is selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, unsubstituted maleimide, maleimide substituted with one or two alkyl groups and 3-sulfo-maleimide and R1 and R2 are the same or different are selected from the group consisting of iodide, bromide, chloride, azide, tosylate,

mesylate, nosylate, triflate, hydrogen, CONH2, carboxyl, hydroxyl, sulfonic acid, tertiary amine, quaternary ammonium, unsubstituted alkyl, substituted alkyl, -COOR', -CONR'2 or COR' wherein the substituents of the substituted alkyl groups are selected from the group consisting of -CONH2, carboxyl, hydroxyl, sulfonic acid, tertiary amine and quaternary ammonium and wherein R' is C1-C6 alkyl or phenyl, or a method for radiolabeling thiol-containing peptides with fluorine-18 (F-18), comprising reacting all peptide comprising a free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate ad triflate, (3) the said method wherein the hapten is all metal chelate complex, (4) the said method wherein the metal chelate complex comprises manganese, iron, or gadolinium, (5) the method mentioned above wherein the bispecific antibody or antibody fragment is *all* monoclonal *all* humanized antibody, and (6) the method mentioned above wherein the F-18-labeled peptide is detected by positron emission tomography.

The specification discloses only a method for detecting a tissue using a specific bispecific or humanized monoclonal antibody or Fab fragment thereof where one arm is specific for a target tissue of the patient and the other arm is specific for an F-18-labeled peptide selected from the group consisting of X-Gly-D-Tyr-D-Trp-Gly-D-Lys(X)-Gly-D-Tyr-DTrp-OH where X represents a free or protected amino acid group, Ac-Cys(Y)-D-Tyr-D-Trp-Gly-D-Cys(Y)-Gly-Dtyr-D-Trp-OH wherein Y represents a free or protected thiol group, and Ac-Gly-D-iodo-Tyr-Trp-Gly-D-Lys(Ac)-Gly-D-Trp-OH by positron emission tomography (PET).

With the exception of the specific F-18-labeled peptides mentioned above, there is insufficient written description about the structure associated with function of all F-18-labeled peptides, *all* low molecular weight hapten conjugated to *all* undisclosed F-18 labeled peptide and *all* bispecific monoclonal or humanized antibody or binding fragment thereof that binds specifically for *all* F-18-labeled peptide. There is inadequate written description about the binding specificity of the bispecific antibody and the immunogen (F-18 labeled peptide) used for making the bispecific antibody for the claimed method. Further, Applicants disclose only three F-18-labeled peptides, there is a lack of a written description of *all* additional F-18-labeled peptide, low molecular weight hapten conjugated F-18-labeled peptide, let alone all bispecific antibodies that binds to all tissue and all F-18-labeled peptide for a method for detecting a tissue by positron emission tomography. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus,

Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

(11) Response to Argument

Claim Rejections - 35 USC § 112 First paragraph enablement

At page 7 of the Brief, Appellant argues that the presently claimed invention is utilized in a wide range of known bispecific antibodies and provides the chemistry to successfully label F-18 onto wide variety of peptides for use in the known methods. The record indicates that a skilled artisan is able to practice the invention across the full scope of claim 9. Neither the fact that the structure of an F-18 labeled peptide is not specified, nor the fact that different peptide sequences produce antibodies that have different binding specificities, leads to a conclusion of lack of enablement for bispecific antibodies and fragments that are specific to an F-18 labeled peptide.

Appellant' arguments have been fully considered but are not found to be persuasive. In contrast to Appellant's assertion that presently claimed invention is utilized in a wide range of known bispecific antibodies, the claimed method of detection requires the use of a bispecific antibody with one arm that is specific to all target tissue of the patient and another arm that is specific to a F-18-labeled peptide, all low molecular weight hapten conjugated to all undisclosed F-18-labeled peptide. However, the binding specificity of the bispecific antibody and the immunogen (F-18 labeled peptide) used for making such bispecific antibody for the claimed method is not taught in the specification as filed. The specification fails to provide sufficient guidance as to the structure of the F18-label peptide, much less about the binding specificity of the bispecific antibody, let alone using the undisclosed bispecific antibody for detecting a tissue in a patient. Kuby et al reference establishes that **antibody specificity** generated from a fragment differs from antibody specificity directed against the native full-length polypeptide. It is known that even a single amino acid difference can affect the binding specificity of the antibody. Colman *et al* teach that even a single amino acid changes within the interface of an antibody-antigen can drastically affect the binding specificity and affinity of the antibody (See page 33, in particular), let alone bispecific antibody that binds to all tissue and all F-18 labeled peptide with unspecified amino acid sequence for the claimed method. In the absence of guidance as to the

specific amino acid residues (the epitope) to which the claimed bispecific antibody binds or makes contact (the binding specificity), it is unpredictable which undisclosed bispecific antibody is useful for the claimed method. Given the indefinite number of undisclosed bispecific antibody for the method of detection, there is a lack of in vivo working example in the specification as filed demonstrating that all undisclosed bispecific antibody could binds specifically to all F-18 peptide and tissue in a patient for the claimed method.

At page 8, first full paragraph of the Brief, Appellant argues that in the clinical setting, fluorine-18 (F-18) is one of the most widely used postron-emitting nuclides and a skilled clinician would be fully enabled to practice PET with the F-18 labeled peptides without in vivo working example. Further, the targeting of antibodies and fragments for imaging is well known in the art.

Appellant' arguments have been fully considered but are not found to be persuasive. The issue here is not whether one of skilled clinician would be fully enabled to practice PET with F-18 labeled peptide, the issue here is whether the bispecific antibody or binding fragment thereof that binds to all target tissue of the patient and all F-18-labeled peptide or low molecular weight hapten conjugated to the undisclosed F-18-labeled peptide in the claimed method is enabled. The specification fails to provide sufficient guidance as to the structure of the F18-label peptide, much less about the binding specificity of the bispecific antibody, let alone using the undisclosed bispecific antibody for detecting a tissue in a patient. Kuby et al reference establishes that **antibody specificity** generated from a fragment differs from antibody specificity directed against the native full-length polypeptide. It is known that even a single amino acid difference can affect the binding specificity of the antibody. Colman *et al* teach that even a single amino acid changes within the interface of an antibody-antigen can drastically affect the binding specificity and affinity of the antibody (See page 33, in particular), let alone bispecific antibody that binds to all tissue and all F-18 labeled peptide with unspecified amino acid sequence for the claimed method. In the absence of guidance as to the specific amino acid residues (the epitope) to which the claimed bispecific antibody binds or makes contact (the binding specificity), it is unpredictable which undisclosed bispecific antibody is useful for the claimed method. Given the indefinite number of undisclosed bispecific antibody for the method of detection, there is a lack of in vivo working example in the specification as filed demonstrating that all undisclosed bispecific antibody could binds specifically to all F-18 peptide and tissue in a patient for the claimed method. Until the time when such bispecific antibody that binds to *all* F-18-labeled peptide and a

targeted tissue is made or identified, then one skilled in the art can use the bispecific antibodies or binding fragment thereof for detection such as PET imaging.

At page 8, second full paragraph of the Brief, Appellant argues that the examiner had no concern with a method of labeling all thiol-containing peptide with F-18, even though the claim encompasses peptides of mall structure. Appellant asserts that the examiner concedes that the making of antibodies to all immunogen is straightforward, and the present specification enables a skilled artisan to make mall different F-18 radiolabeled peptides, then the present claims to methods of detecting tissue using these bispecific antibodies and fragments to the radiolabeled peptides must be enabled.

Appellant' arguments have been fully considered but are not found to be persuasive. The claims in instant application are drawn to a method for detecting a tissue comprising: (a) administering to a patient a genus of undisclosed bispecific antibody or antibody fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to all F-1 8-labeled peptide or all low molecular weight hapten conjugated to the F-18-labeled peptide; and allowing the bispecific antibody or antibody fragment lo bind to the target tissue, and the non-targeted bispecific antibody or antibody fragment to clear; (b) administering the F-1 8-labeled peptide or the hapten conjugate thereof to the patient, and allowing the F-18-labeled peptide or the hapten conjugate thereof to bind to the bispecific antibody or the antibody fragment, and the unbound F18-labeled peptide or hapten conjugate thereof to clear; and (c) detecting the F-1 8-labeled peptide, thereby detecting the target tissue. The claims are NOT drawn to a method of F-18 radiolabeling a peptide or a method of detection using F-18 radiolabeled peptide or F-18 radiolabeling antibody wherein the antibody is known in the art. Until the time when such bispecific antibody that binds to *all* F-18-labeled peptide and targeted tissue is made or identified, then one skilled in the art can use the bispecific antibodies or binding fragment thereof for imaging for the claimed method.

At paragraph bridging page 8 and 9, Appellant argues that the specification provides a written description of the invention. Appellant has demonstrated possession of the full scope of the genus defined in claim 9 in accordance with the USPTO Written Description Guidelines. Once possession of the genus of F-18 labeled peptides is demonstrated, possession of bispecific antibodies specific to these peptides necessarily must follow. The specification describes the

genus of F-18 labeled peptides in great detail, and thus an adequate written description of all claims is contained within appellant's disclosure.

Appellant' arguments have been fully considered but are not found to be persuasive. The specification discloses only a method for detecting a tissue using a specific bispecific or humanized monoclonal antibody or Fab fragment thereof where one arm is specific for a target tissue of the patient and the other arm is specific for an F-18-labeled peptide selected from the group consisting of X-Gly-D-Tyr-D-Trp-Gly-D-Lys(X)-Gly-D-Tyr-DTrp-OH where X represents a free or protected amino acid group, Ac-Cys(Y)-D-Tyr-D-Trp-Gly-D-Cys(Y)-Gly-Dtyr-D-Trp-OH wherein Y represents a free or protected thiol group, and Ac-Gly-D-iodo-Tyr-Trp-Gly-D-Lys(Ac)-Gly-D-Trp-OH by positron emission tomography (PET). Other than the specific F-labeled peptide for the claimed method of detection, there is inadequate written description about the structure and function of all F-labeled peptide, including the binding specificity of bispecific antibody and immunogen used for making such bispecific antibody that are critical for the claimed method. The disclosure as written is merely extending an invitation for one skilled in the art for further experimentation for the claimed method.

At pages 9-13 of the Brief, Appellant argues that the making of antibodies to all immunogen is a straightforward and routine matter. Appellant cites various references such as US Patent 5,256,395 for teaching monoclonal mouse antibodies to an In(III)-diDTPA which is a low molecular weight hapten, Orlandi et al for general techniques for cloning murine immunoglobulin variable domains, various references for producing humanized Mabs such as Jones et al, Riechmann et al, Verhoeyen et al, Carter et al, Sandhu et al, and Singer et al. Appellant cites Mendex et al for teaching fully human antibodies from transgenic nonhuman animal. Thus, a skilled artisan readily can generate antibodies to all immunogen, and from those antibodies can prepare antibody fragments that are specific to the immunogen. The fact that different peptide sequences produce antibodies that have different specificities does not lead to a lack of enablement of the present claims, since a skilled artisan could generate an antibody for all peptide, without event knowing the amino acid sequence of the peptide.

Appellant' arguments have been fully considered but are not found to be persuasive. The claims in instant application are drawn to a method for detecting a tissue comprising: (a) administering to a patient a genus of undisclosed bispecific antibody or antibody fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific

to all F-1 8-labeled peptide or all low molecular weight hapten conjugated to the F-18-labeled peptide; and allowing the bispecific antibody or antibody fragment lo bind to the target tissue, and the non-targeted bispecific antibody or antibody fragment to clear; (b) administering the F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing the F-18-labeled peptide or the hapten conjugate thereof to bind to the bispecific antibody or the antibody fragment, and the unbound F18-labeled peptide or hapten conjugate thereof to clear; and (c) detecting the F-18-labeled peptide, thereby detecting the target tissue.

The specification discloses only a method of labeling peptide or thiol containing peptide with F-18 fluorinated alkene. The specification merely mentions a method for detecting a tissue using a specific bispecific or humanized monoclonal antibody or Fab fragment thereof wherein one arm is specific for a target tissue of the patient and the other arm is specific for an F-18-labeled peptide (page 3). The specification on page 4 discloses the bispecific monoclonal antibody (bsMAb) or bispecific Fab fragment is from monoclonal or humanized and the F-18 labeled peptide is selected from the group consisting of X-Gly-D-Tyr-D-Trp-Gly-D-Lys(X)-Gly-D-Tyr-DTrp-OH where X represents a free or protected amino acid group, Ac-Cys(Y)-D-Tyr-D-Trp-Gly-D-Cys(Y)-Gly-Dtyr-D-Trp-OH wherein Y represents a free or protected thiol group, and Ac-Gly-D-iodo-Tyr-Trp-Gly-D-Lys(Ac)-Gly-D-Trp-OH by positron emission tomography (PET). Other than the specific F-18 peptide mentioned above that could be used as immunogen for bispecific antibody for the claimed method of detection, there is insufficient guidance as to the binding specificity of *all* bispecific antibody such as humanized monoclonal antibody or Fab fragment thereof where one arm is specific for *all* target tissue of the patient and the other arm is specific for *all* undisclosed F-18-labeled peptide, *all* low molecular weight hapten conjugated to *all* F-18-labeled peptide mentioned above for a method for PET imaging. There is also insufficient guidance with regard to the structure such as the amino acid sequence of all F-18 labeled peptide, all F-18 labeled peptide contains a thiol group, all F-18 labeled peptide labeled by reacting all peptide comprising a free thiol group with a labeling reagent having the general formula as set forth in claims 11-12, all low molecular weight hapten conjugated to all F-18 labeled peptide, all low molecular weight hapten conjugated to all F-18 labeled peptide wherein the hapten is all metal chelate complex such as the ones recited in claim 17 to which the bispecific antibody such as monoclonal or humanized bispecific antibody binds in the claimed method. Given the indefinite number of undisclosed F-18 labeled peptide and without the amino acid sequence, it is unpredictable which undisclosed bispecific antibody such as monoclonal

antibody generated form the undisclosed F-18 labeled peptide would bind to all F-18 labeled peptide for the claimed method.

Other than the specific F-18 labeled peptides mentioned above that could be used as immunogen for the bispecific antibody in the claimed method, there is insufficient guidance about the structure (amino acid residues) of all of F-18 labeled peptide, in turn, would be useful for making the bispecific antibody for the claimed method. Without the specific amino acid residues, one of skilled in the art cannot even contemplate of making such bispecific antibody that would have one arm specific for all F-18 labeled peptide and one arm would be specific for all tissue in a patient. Given the indefinite number of undisclosed bispecific antibody, it is unpredictable which undisclosed bispecific antibody would bind specifically to all undisclosed F-18 peptide and a target tissue for the claimed method.

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Colman *et al* teach that even a single amino acid changes within the interface of an antibody-antigen can raise or lower the affinity of the antibody (See page 33, in particular).

Given the indefinite number of undisclosed bispecific antibody in the claimed method, there is no vivo working examples demonstrating that all bispecific antibodies with unknown specificity would be useful for a method of detecting a tissue in a patient using PET. Since the binding specificity of the bispecific antibody such as monoclonal antibody that is specific for all F-18 labeled peptide is not enabled, it follows that all antibody fragment thereof, all humanized antibody or fragment thereof for the claimed method is not enabled. Given the indefinite number of undisclosed bispecific antibody and F-18 labeled peptide, it is unpredictable which undisclosed bispecific antibody would bind specifically to the undisclosed F-18 labeled peptide, in turn, would be useful for all purpose. Since the F-18 labeled peptide without the specific amino acid is not enabled, it follows that *all* low molecular weight hapten conjugated to *all* undisclosed F-18 labeled peptide for making the bispecific antibody that would bind specifically to the undisclosed F-18 labeled peptide, in turn, useful for the claimed method is not enabled. It also follows that the method of labeling all undisclosed peptide and all metal chelate complex to all undisclosed peptide for making the bispecific antibody that would bind specifically to the undisclosed F-18 labeled peptide, in turn, useful for the claimed method is not enabled. Until the structure of the F-

18 labeled peptide is disclosed, one skilled in the art could not make all bispecific antibody using all of the references cited by appellant, much less use all the undisclosed bispecific antibody or fragment thereof for the claimed method. Even if the F-18 peptide is limited to the ones recited in claims 13-15, there is insufficient guidance and working example regarding the binding specificity of the bispecific antibody in the claimed method such as whether the bispecific antibody would bind to all F-18 labeled peptide. Not only the structure of all F-18 labeled peptide in claims 11 and 12 are not enabled for the reasons above, the term "comprising" is open-ended. It expands the undisclosed peptide to include additional amino acids at either or both ends in addition to having a free thiol group with a labeling reagent such as F-18 fluorinated alkene. There is insufficient guidance as to what are the undisclosed amino acids to be added and whether the peptide maintained its structure and function, let alone generating bispecific antibody that has the same binding specificity as the unmodified peptide, in turn, useful for the claimed method. Until the binding specificity of the bispecific antibody and the structure of the F-18 labeled peptide in the claimed method are taught, the specification is merely an invitation to one skilled in the art for further experimentation. Since it is unpredictable as to which undisclosed "bispecific antibody" such as monoclonal antibody, humanized antibody or binding fragment thereof in the claimed method would bind specifically to other "F-18 labeled peptide", the experimentation left to those skilled in the art is unnecessarily, improperly, extensive and undue. Finally, none of the cited references mentioned above teach bispecific antibody or antibody fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to all F-18 labeled peptide or low molecular weight hapten conjugated to the F-18-labeled peptide for the claimed method. In fact, it is its short half-life of F-18 that has limited or precluded its use with longer-lived specific targeting vectors such as antibodies, antibody fragments, recombinant antibody constructs and longer-lived receptor-targeted peptides (page 1, line 17 of the specification and page 15 of the brief), let alone making all bispecific antibody with an arm that binds specifically to a target tissue of the patient and another arm that binds specific to all F-18 labeled peptide.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance for the F-labeled peptide and the binding specificity of the bispecific antibody in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

At page 13, first full paragraph of the Brief, Appellant argues that the term "F-18 labeled peptide" in claim 9, covers peptides with differing numbers of amino acid residues, and thus "expands" the scope of the claimed peptide. Thus, the language expands the teaching to that which is not described.

Appellant' arguments have been fully considered but are not found to be persuasive. Not only the structure of all F-18 labeled peptide in claims 11-12 and claims dependent therefrom are not enabled for the reasons above, the term "comprising" is open-ended. It expands the undisclosed peptide to include additional amino acids at either or both ends in addition to having a free thiol group with a labeling reagent such as F-18 fluorinated alkene. There is insufficient guidance as to what are the undisclosed amino acids to be added and whether the peptide maintained its structure and function, let alone generating bispecific antibody that has the same binding specificity as the unmodified peptide, in turn, useful for the claimed method. Until the binding specificity of the bispecific antibody and the F-18 labeled peptide in the claimed method are taught, the specification is merely an invitation to one skilled in the art for further experimentation. Since it is unpredictable as to which undisclosed "bispecific antibody" such as monoclonal antibody, humanized antibody or binding fragment thereof in the claimed method would bind specifically to other "F-18 labeled peptide", the experimentation left to those skilled in the art is unnecessarily, improperly, extensive and undue.

At paragraph bridging page 13 and 14 of the brief, Appellant cites US 4,925,648 for teaching polyspecific antileukocyte antibody conjugate for targeting foci of leukocyte accretion comprises an immunoreactive polyspecific composite of at least two different substantially monospecific antibodies or antibody fragments, conjugated to at least one imaging agent, wherein at least two of said antibodies or antibody fragments specifically bind to different Leukocyte cell types and U,S. Patent No. 5,364,612 for teaching a method of detecting and imaging cardiovascular lesions such as atherosclerotic plaques, vascular clots including thrombi and

emboli, myocardial infarction, and other organ infarcts, using multispecific antibody imaging agent conjugates specific for at least two different antigens.

Appellant' arguments have been fully considered but are not found to be persuasive. It is noted that none of the bispecific antibody taught by the '648 patent and the '612 patent are specific for F18-labeled peptide and target tissue as required by the claimed method.

At pages 14-15 of the Brief, Appellant argues that there are no additional reasons in support of five of the six assertions provided below: (1) the F-18 labeled contains a thiol group (claims 10 and 12); (2) the F-l8-labeled peptide is labeled by a method comprising reacting a peptide comprising a free thiol group with a labeling reagent having the general formula 18F-(CH2)m-CR1 R2-(CH2)n-X (claim 11); (3) the hapten is all metal chelate complex (claim 1 6); (4) the metal chelale (claim 17); complex comprises manganese, iron or gadolinium (5) the bispecific antibody or antibody fragment is all monoclonal or all humanized antibody (claims 1 8 and 1 9); and (6) the F-18 labeled peptide is detected by positron emission tomography (claim 20). As detailed in the background of appellant's specification, in the clinical setting, fluorine-l8 (F-1 8) is one of the most widely used positron-emitting nuclides. It is its short half-life of F-1 8 that has limited or precluded its use with longer-lived specific targeting vectors such as antibodies, antibody fragments, recombinant antibody constructs and longer-lived receptor-targeted peptides. The present invention provides a simple, efficient method for incorporating the F-18 radionuclide into the peptide containing targeting vectors such as proteins, antibodies, antibody fragments, and receptor-targeted peptides, to allow the use of such targeting vectors in routine clinical positron emission tomography.

Appellant' arguments have been fully considered but are not found to be persuasive.

The claims in instant application are drawn to a method for detecting a tissue comprising: (a) administering to a patient a genus of undisclosed bispecific antibody or antibody fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to all F-1 8-labeled peptide or all low molecular weight hapten conjugated to the F-18-labeled peptide; and allowing the bispecific antibody or antibody fragment lo bind to the target tissue, and the non-targeted bispecific antibody or antibody fragment to clear; (b) administering the F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing the F-18-labeled peptide or the hapten conjugate thereof to bind to the bispecific antibody or the antibody fragment, and the unbound F18-labeled peptide or hapten conjugate thereof to clear; and (c)

detecting the F-18-labeled peptide, thereby detecting the target tissue. The critical issue here is the bispecific antibody or fragment thereof in the claimed method and whether the specification enable one skilled in the art how to make and use the claimed invention.

The specification discloses only a method of labeling peptide or thiol containing peptide with F-18 fluorinated alkene. The specification merely mentions a method for detecting a tissue using a specific bispecific or humanized monoclonal antibody or Fab fragment thereof wherein one arm is specific for a target tissue of the patient and the other arm is specific for an F-18-labeled peptide (page 3). The specification on page 4 discloses the bispecific monoclonal antibody (bsMAb) or bispecific Fab fragment is from monoclonal or humanized and the F-18 labeled peptide is selected from the group consisting of X-Gly-D-Tyr-D-Trp-Gly-D-Lys(X)-Gly-D-Tyr-DTrp-OH where X represents a free or protected amino acid group, Ac-Cys(Y)-D-Tyr-D-Trp-Gly-D-Cys(Y)-Gly-Dtyr-D-Trp-OH wherein Y represents a free or protected thiol group, and Ac-Gly-D-iodo-Tyr-Trp-Gly-D-Lys(Ac)-Gly-D-Trp-OH by positron emission tomography (PET). However, there is insufficient guidance as to the binding specificity of *all* bispecific antibody such as humanized monoclonal antibody or Fab fragment thereof where one arm is specific for *all* target tissue of the patient and the other arm is specific for *all* undisclosed F-18-labeled peptide, *all* low molecular weight hapten conjugated to *all* F-18-labeled peptide mentioned above for a method for PET imaging. There is also insufficient guidance with regard to the structure such as the amino acid sequence of all F-18 labeled peptide, all F-18 labeled peptide contains a thiol group, all F-18 labeled peptide labeled by reacting all peptide comprising a free thiol group with a labeling reagent having the general formula as set forth in claims 11-12, all low molecular weight hapten conjugated to all F-18 labeled peptide, all low molecular weight hapten conjugated to all F-18 labeled peptide wherein the hapten is all metal chelate complex such as the ones recited in claim 17 to which the bispecific antibody such as monoclonal or humanized bispecific antibody binds in the claimed method. Given the indefinite number of undisclosed F-18 labeled peptide and without the amino acid sequence, it is unpredictable which undisclosed bispecific antibody such as monoclonal antibody generated form the undisclosed F-18 labeled peptide would bind to all F-18 labeled peptide for the claimed method.

Other than the specific F-18 labeled peptides mentioned above that could be used as immunogen for the bispecific antibody in the claimed method, there is insufficient guidance about the structure (amino acid residues) of all of F-18 labeled peptide, in turn, would be useful for making the bispecific antibody for the claimed method. Without the specific amino acid residues,

one of skilled in the art cannot even contemplate of making such bispecific antibody that would have one arm specific for all F-18 labeled peptide and one arm would be specific for all tissue in a patient. Given the indefinite number of undisclosed bispecific antibody, it is unpredictable which undisclosed bispecific antibody would bind specifically to all undisclosed F-18 peptide and a target tissue for the claimed method.

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Colman *et al* teach that even a single amino acid changes within the interface of an antibody-antigen can raise or lower the affinity of the antibody (See page 33, in particular).

Given the indefinite number of undisclosed bispecific antibody in the claimed method, there is no vivo working examples demonstrating that all bispecific antibody with unknown specificity would be useful for a method of detecting a tissue in a patient using PET. Since the binding specificity of the bispecific antibody such as monoclonal antibody that is specific for all F-18 labeled peptide is not enabled, it follows that all antibody fragment thereof, all humanized antibody or fragment thereof for the claimed method is not enabled. Given the indefinite number of undisclosed bispecific antibody and F-18 labeled peptide, it is unpredictable which undisclosed bispecific antibody would bind specifically to the undisclosed F-18 labeled peptide, in turn, would be useful for all purpose. Since the F-18 labeled peptide without the specific amino acid is not enabled, it follows that *all* low molecular weight hapten conjugated to *all* undisclosed F-18 labeled peptide for making the bispecific antibody that would bind specifically to the undisclosed F-18 labeled peptide, in turn, useful for the claimed method is not enabled. It also follows that the method of labeling all undisclosed peptide and all metal chelate complex to all undisclosed peptide for making the bispecific antibody that would bind specifically to the undisclosed F-18 labeled peptide, in turn, useful for the claimed method is not enabled. Until the structure of the F-18 labeled peptide is disclosed, one skilled in the art could not make all bispecific antibody using all of the references cited by appellant, much less use all the undisclosed bispecific antibody or fragment thereof for the claimed method. Even if the F-18 peptide is limited to the ones recited in claims 13-15, there is insufficient guidance and working example regarding the binding specificity of the bispecific antibody in the claimed method such as whether the bispecific antibody would bind to all F-18 labeled peptide. Not only the structure of all F-18 labeled

peptide in claims 11 and 12 are not enabled for the reasons above, the term "comprising" is open-ended. It expands the undisclosed peptide to include additional amino acids at either or both ends in addition to having a free thiol group with a labeling reagent such as F-18 fluorinated alkene. There is insufficient guidance as to what are the undisclosed amino acids to be added and whether the peptide maintained its structure and function, let alone generating bispecific antibody that has the same binding specificity as the unmodified peptide, in turn, useful for the claimed method. Until the binding specificity of the bispecific antibody and the structure of the F-18 labeled peptide in the claimed method are taught, the specification is merely an invitation to one skilled in the art for further experimentation. Since it is unpredictable as to which undisclosed "bispecific antibody" such as monoclonal antibody, humanized antibody or binding fragment thereof in the claimed method would bind specifically to other "F-18 labeled peptide", the experimentation left to those skilled in the art is unnecessarily, improperly, extensive and undue. Finally, none of the cited references mentioned above teach bispecific antibody or antibody fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to all F-18 labeled peptide or low molecular weight hapten conjugated to the F-18-labeled peptide for the claimed method. In fact, it is its short half-life of F-18 that has limited or precluded its use with longer-lived specific targeting vectors such as antibodies, antibody fragments, recombinant antibody constructs and longer-lived receptor-targeted peptides (page 1, line 17 of the specification and page 15 of the brief), let alone making all bispecific antibody with an arm that binds specifically to a target tissue of the patient and another arm that binds specific to all F-18 labeled peptide.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance for the F-labeled peptide and the binding specificity of the bispecific antibody in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

At paragraph bridging page 15 and 16 of the brief, Appellant argues that there the examiner's position with respect to the enablement in this case is at odds with the position she took on this issue in the parent application, now US 6,358,489. The examiner had no concern with a method of labeling all thiol-containing peptide with F-18, even though the claim encompasses peptides of mall structures. Appellant contends that since the examiner concedes that the making of antibodies to all immunogen is straightforward, and the present specification enables the skilled artisan to make mall different F-18 radiolabeled peptides, then the present claims to methods of detecting tissue using these antibodies to the radiolabeled peptides necessarily must be enabled.

Appellant' arguments have been fully considered but are not found to be persuasive. Every case is examined on its own merit. The claims in instant application are drawn to a method for detecting a tissue comprising: (a) administering to a patient a genus of undisclosed bispecific antibody or antibody fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to all F-1 8-labeled peptide or all low molecular weight hapten conjugated to the F-18-labeled peptide; and allowing the bispecific antibody or antibody fragment lo bind to the target tissue, and the non-targeted bispecific antibody or antibody fragment to clear; (b) administering the F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing the F-18-labeled peptide or the hapten conjugate thereof to bind to the bispecific antibody or the antibody fragment, and the unbound F18-labeled peptide or hapten conjugate thereof to clear; and (c) detecting the F-18-labeled peptide, thereby detecting the target tissue. However, the claims are not drawn to a method of radiolabeling thiol-containing peptide with fluorine-18, such as the claims in the issued patent. Although the method of making antibodies to all immunogen is straightforward, the structure of the immunogen such as the specific F-18 labeled peptide used by appellant to make such antibody that would bind to all F-18 peptide must be taught. Until the binding specificity of the bispecific antibody in the claimed method is enabled, the disclosure merely extends an invitation for one skilled in the art for further experimentation.

Claim Rejections - 35 USC § 112 First paragraph Written Description

At pages 16-17 of the Brief, Appellant reiterates the USPTO Written Description Guidelines and argues that what constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number "depends

on whether one of skill in the art would recognize that the appellant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.

Appellant' arguments have been fully considered but are not found to be persuasive. The claims in instant application are drawn to a method for detecting a tissue comprising: (a) administering to a patient a genus of undisclosed bispecific antibody or antibody fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to all F-1 8-labeled peptide or all low molecular weight hapten conjugated to the F-18-labeled peptide; and allowing the bispecific antibody or antibody fragment lo bind to the target tissue, and the non-targeted bispecific antibody or antibody fragment to clear; (b) administering the F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing the F-18-labeled peptide or the hapten conjugate thereof to bind to the bispecific antibody or the antibody fragment, and the unbound F18-labeled peptide or hapten conjugate thereof to clear; and (c) detecting the F-18-labeled peptide, thereby detecting the target tissue. However, the specification discloses only a method for detecting a tissue using a specific bispecific or humanized monoclonal antibody or Fab fragment thereof where one arm is specific for a target tissue of the patient and the other arm is specific for an F-18-labeled peptide selected from the group consisting of X-Gly-D-Tyr-D-Trp-Gly-D-Lys(X)-Gly-D-Tyr-DTrp-OH where X represents a free or protected amino acid group, Ac-Cys(Y)-D-Tyr-D-Trp-Gly-D-Cys(Y)-Gly-Dtyr-D-Trp-OH wherein Y represents a free or protected thiol group, and Ac-Gly-D-iodo-Tyr-Trp-Gly-D-Lys(Ac)-Gly-D-Trp-OH by positron emission tomography (PET).

There is inadequate written description about the structure associated with function such as the binding specificity of the bispecific antibody such as monoclonal or humanized antibody or binding fragment thereof in the claimed method of detection. Further, there is inadequate written description about the structure associated with function such as amino acid sequence of the immunogen such as F-18 labeled peptide, low molecular weight hapten conjugated F-18-labeled peptide including F-18 labeled peptide containing thiol group used by appellant for making the bispecific antibody for the claimed method. Further, Appellant disclose only three F-18-labeled peptides, there is a lack of a written description of *all* additional F-18-labeled peptide, low molecular weight hapten conjugated F-18-labeled peptide, let alone all bispecific antibody or fragment thereof that binds to all tissue and all F-18-labeled peptide for a method for detecting a tissue by positron emission tomography as broadly as claimed. Until the binding specificity of

the bispecific antibody and the F-18 labeled peptide in the claimed method are adequately described, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

At pages 18-19 of the Brief, Appellant argues that the species of claims 13-15 have been found by the examiner to be allowable, and only the genus claims are rejected. The genus defines bispecific antibodies and fragments in which one arm is specific to a targeted tissue and the other arm is specific to an "an F-18 labeled peptide or a low molecular weight hapten conjugated to the F-18-labeled peptide". The level of skill in the antibody technology is very high. Once possession of the genus of F-18 labeled peptide is demonstrated, possession of bispecific antibodies and fragments specific to these peptides necessarily must follow. The only issue is whether the specification sufficiently describes the genus of F-18 labeled peptides. The specification provides a simple and efficient method for incorporating the F-18 radionuclide into peptide containing targeting vectors such as proteins, antibodies, antibody fragments and receptor-targeted peptides. Of all nucleophiles present on peptides, only a free thiol group can be rapidly alkylated at neutral pH and moderate temperature. The specification teaches a method for labeling all thiol-containing peptide and then making an antibody to that peptide. Since the level of skill in this art is very high, and antibodies can be made against virtually all protein", appellants' possession of bispecific antibodies and fragments in which one arm is specific to an F-18 labeled peptide is manifest.

Appellant' arguments have been fully considered but are not found to be persuasive. In contrast to appellant's assertion that the only issue is whether the specification sufficiently describes the genus of F-18 labeled peptides, the critical issue here is whether appellant has possession of the bispecific antibody such as monoclonal antibody, humanized antibody or fragment thereof that binds to all F-18 labeled peptide and tissue for the claimed method. Until the structurally feature such as the binding specificity of bispecific antibody and the structure such as the amino acid sequence of the antigen such as F-18 labeled peptide or low molecular weight hapten conjugated to the F-18-labeled peptide have been adequately described, a person of

ordinary skill in the antibody art lacks a reasonable expectation of success of obtaining all bispecific antibody that binds to all F-18 peptide and all tissue given the state of the art at the time as evident by the teachings of Kuby *et al* and Colman et al discussed supra. Further, given the specification discloses only three species of F-18 labeled peptide as set forth in claims 13-15, the other undisclosed F-18 labeled peptide or low molecular weight hapten conjugated F-18 labeled peptide including the ones recited in claims 10-17 for the claimed method is not adequately described. Since the structure of the other undisclosed F-18 labeled peptide has not been adequately described, antibodies to such undisclosed F-18 peptide cannot be made, much less for using such bispecific antibody for the claimed invention.

At pages 20-21 of the Brief, Appellant argues that there is a separate basis for patentability of each of claims 10, 11 and 12 based on the lack of enablement and written description. Claim 11 defines a generic formula indicating with specificity a subgenus of F-18 labeled peptides. Detailed guidance is provided in the specification regarding how to prepare F-18 labeled peptide and therefore an additional basis for enablement exists as to claim 11. While claims 10 and 12 do not include a generic formula, they do define subgenera of the genus defined in claim 9.

Appellant' arguments have been fully considered but are not found to be persuasive. The critical issue here is whether appellant has possession of the bispecific antibody such as monoclonal antibody, humanized antibody or fragment thereof that binds to all F-18 labeled peptide and tissue for the claimed method. Until the structurally feature such as the binding specificity of bispecific antibody and the structure such as the amino acid sequence of the antigen such as F-18 labeled peptide or low molecular weight hapten conjugated to the F-18-labeled peptide have been adequately described, a person of ordinary skill in the antibody art lacks a reasonable expectation of success of obtaining all bispecific antibody that binds to all F-18 peptide and all tissue given the state of the art at the time as evident by the teachings of Kuby *et al* and Colman et al discussed supra. Although Claim 11 defines a generic formula indicating with specificity a subgenus of F-18 labeled peptides, a peptide without the amino acid sequence has no structure, much less function. Thus the F-18 labeled peptide is not adequately described, regardless whether the peptide contains a thiol group or not. The same principle can be applied to claims 11-12. Since the F-18 labeled peptide containing the thiol group or labeled by a method as set forth in claims 11 and 12 is not adequately described, antibodies to such undisclosed F-18

peptide cannot be made, much less for using such bispecific antibody for the claimed invention. Until the binding specificity or the epitope to which the bispecific antibody binds is described, the method of detection using the bispecific antibody comprising one arm that is specific to all F-18 peptide and another arm that is specific to all target tissue is not adequately described.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Phuong N. Huynh, Ph.D.
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Conferees
Christina Chan
SPE, Art unit 1644

Christopher Low
SPE, Art unit 1653

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600